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IODINE IN NUTRITION

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IODINE IN NUTRITION

By E. B. ASTWOOD, M.D., Ph.D.*

Iodine is regarded as one of the essential trace elements, that is, one of the elements occurring in only small amounts in the body, being derived from the traces present in foods and needed for the health and well being of the individual. Other familiar trace elements are iron, copper, zinc, cobalt, manganese, and perhaps fluorine, and molybdenum. The only known use to which iodine is put by the body is in the manufacture of thyroxine, the hormone of the thyroid gland. Each molecule of this hormone contains four atoms of iodine—about two-thirds of its weight—and consequently without iodine, thyroxine could not be made. The fact that iodine deficiency is related to goiter is widely recognized by the general public and there has been an increasing acceptance of plans to increase the intake of iodine artificially by the use of iodized salt. Popular opinion has extended the belief in the benefits from iodized salt to the belief that iodine can promote wellbeing and a variety of magical cures of human illness, including reversal of the changes attendant upon advancing age. Given in large amounts iodine exerts effects which may be of benefit in certain disease states, but the normal role of iodine in the body is to provide an essential element for thyroxine synthesis.

We are told that iodine when discovered in 1811 by the French chemist, Courtois, was so named from the Greek word meaning violet. To most, iodine means the brown, malodorous tincture applied with such pain to cuts. But iodine was so named because of the color of the vapor formed when the element is heated and has come to be used as a generic term for the substance even when it is chemically transformed and combined in other compounds. To the chemist iodine means only the element, and he writes it I_2; the reduced form is termed iodide and written I^- indicating that it has one extra negative charge or electron and it is then in a chemical state equivalent to the chloride of table salt. The body derives its iodine from the small amounts present in foods. These foods in turn are ultimately dependent for their iodine content upon that present in soils and waters. It has been pointed out by McHenry (1) that the relationship between iodine and goiter "is the only accepted link between soil composition and human disease."

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Iodine Requirement

It has been estimated that the normal human body contains about nine mg. of iodine of which eight are in the thyroid gland and one in the rest of the body (2). At least 99% of all this iodine is in the form of iodinated organic compounds and 1%, or perhaps much less, is iodide ion. During development and growth this quantity must be accumulated and losses from the body must be constantly replaced.

There have been a number of estimates made of the minimal and optimal requirements of man for iodine. It has been difficult to arrive at conclusive figures; indeed it is probable that the daily requirement is not fixed but rather a variable dependent upon a number of factors, some of which will be considered later. Earlier estimates, based upon the quantity of iodine excreted daily by normal individuals yielded values below 50 and as low as 10 μg. of iodine daily. Some of these studies were conducted in regions of borderline or low iodine abundance and are now considered to be too low. In several parts of the world including the United States a limited number of analyses of urinary iodine excretion have given values between 100 and 200 μg. daily (3, 2). It is regrettable that there are so few data on iodine excretion in contrast to the vast collections of analyses on waters, soils, rocks and living things. The quantity of iodine excreted accurately reflects iodine intake; its measurement involves a relatively simple procedure, and it is far more meaningful than estimates of iodine intake based upon the inaccurate and laborious determination of the iodine content of the food.

Estimates of iodine requirement have also been based upon the quantity of thyroid hormone needed daily and the quantity normally manufactured and secreted daily by the thyroid gland. It has been variously estimated that between 200 and 400 μg. of thyroxine daily are required to restore the myxedematous patient to normal. By using radioactive iodine, estimates can be made of the rate at which iodine is incorporated into the thyroid gland and the rate at which thyroxine is broken down in the tissues. Such studies also indicate that as little as 200 μg. or less and up to 400 μg. of thyroxine may be made, secreted, and used up each day (4, 5). As thyroxine is two-thirds iodine, roughly 150 to 300 μg. of iodine would be involved in these transformations. About one-third of the iodine released from spent thyroxine is reused. It might thus be estimated than 100 to 200 μg. would be needed each day for normal thyroxine synthesis. The excellent agreement between these estimates, arrived at in such different ways, accounts for the acceptance of 100 to 200 μg. as the human daily requirement for iodine.

Consideration of the relatively large quantity of iodine normally stored in the thyroid gland makes it plain that alterations in the dietary intake of

iodine may only slowly cause changes in iodine metabolism. Were it possible completely to deplete the body of iodine, reaccumulation of the normal 9 mg. would require many months after the daily intake of 100 μg. was resumed. McClendon (6) has estimated that "it would take a person 2,500 years to collect a normal supply of iodine by drinking Lake Superior water or 6 years by eating a normal Minneapolis diet."

Industrial Sources of Iodine

Iodine is among the rarest elements of the earth's crust and in only a very few places is it sufficiently concentrated to make extraction feasible on a large scale. Its concentration is thought to have been effected largely by living things rather than by physico-chemical forces. Seaweeds, the first commercial source, as well as sponges and corals, may contain 0.1% of iodine and the dried powders derived therefrom about 1% (7, 8). Some of this iodine is in organic combination and the same iodinated amino acids as those found in the thyroid gland have been detected in these lower forms of plant and animal life (9, 10). A marine plant source of iodine is thought also to account for the iodide in the salt brines of oil wells in the East Indies, California, and Italy; these waters contain from 0.05% to 0.1% of iodide which can be economically recovered. The largest source of iodine is the caliche of northern Chili where it occurs to the extent of about 0.15% as sodium iodate in the Chilean saltpeter. To obtain the iodate the crushed caliche is extracted with hot water; upon cooling the sodium nitrate crystallizes out and from the mother liquors iodine is precipitated upon reduction of the iodate with sodium bisulfite. The crude iodine is then purified to better than 99% by sublimation and shipped as elemental iodine in 70 Kg. wooden kegs covered with cowhide (11). Chilean nitrate is only partly freed of iodate, the commercial product containing about 0.02%, and is a source of iodine for soils and crops.

Dietary Sources

The iodine content of most foods (7, 12) is so low that accurate chemical analysis is difficult; the values obtained have varied widely and many of the earlier analyses have probably been too high. Vegetable products in general have a low iodine content which is dependent to some extent upon the soils on which they are grown. Vegetarian diets would usually provide less than 100 μg. of iodine daily unless dairy products were also included. Fresh vegetables and fruits contain about 20 to 30 μg./Kg.; wheat, corn, and other grains and cereals contain somewhat more, perhaps 50 μg./Kg., but because of their low water content the quantity eaten is relatively small. Conversely,

milk which may contain only 35 μg./Kg. can provide an appreciable portion of the daily requirement because a quart or more may be taken daily. This also applies to meat, which though nearly as low in iodine as wheat, would provide about 5 times as much iodine on an equicaloric basis. Eggs, butter, animal fats and cheeses usually contain somewhat more iodine, up to 100 μg./Kg., but again these are concentrated foods eaten in small amounts. Prepared foods usually contain very much less iodine; sugar, white flour, boiled rice, and vegetable oils may be very low in iodine and, at the same time, they may make up an appreciable portion of the daily caloric intake.

The only rich sources of iodine commonly included in the human dietary are those derived from marine animals. Sea fish contain 200 to 1000 μg./Kg. and shellfish (mollusks and crustaceans) a similiar or slightly larger amount. Inclusion of fish in the diet once daily would thus provide an abundant iodine intake and it is probably this source more than any other which accounts for the finding that populations near the sea receive more iodine than those farther inland. The problem of obtaining sufficient iodine from food of non-marine origin may be seen from values shown in Table I. Iodine-rich seaweed is an abundant source on a limited scale for some peoples. Kelp contains about 200,000 μg./Kg. and the dried kelp meal nearly ten times as much, or 0.1% to 0.2% of iodine (7, 8, 12). Used as a condiment this would provide ten times as much iodine as American iodized salt.

TABLE I.

Approximate quantity of common foods needed to supply 100 μg. of iodine.*

FOODSTUFF	POUNDS OF FRESH PRODUCT
Vegetables, Fruits	10.
Cereals, Grains, Nuts	8.
Meat, Freshwater Fish, Fowl	6.
Milk	4.
Eggs	2.
Marine Fish	0.3
Shellfish	0.2

*Estimates derived from data given in references 7 and 12.

Drinking water is seldom a significant source of iodine, the content usually being a few micrograms per liter or less. Some well waters and those

from some mineral springs contain appreciable quantities of iodine (7), but such waters often have either a high salt content or unpalatable ingredients such as sulfide, and thus are not widely used.

Iodized Salt

Provision of supplements of iodine to populations of goitrous areas has been accomplished on a limited scale by the periodic administration of a measured quantity in the form of a tablet or in candy. This method has been found feasible in the case of school children but not practicable for the population as a whole. The only method which has become widely accepted has been the addition of iodine, usually in the form of potassium iodide, to the salt used for cooking and seasoning. The proper quantity of iodine to be added is still a subject of debate, and as shown in Table II, various countries have adopted quite different concentrations. American iodized salt, with the highest content, would provide an abundance of iodine even if its use were restricted to that salt added at the table, while that of Switzerland would have to be used for all purposes of food preparation and manufacture to meet the minimal needs for iodine.

TABLE II.

Iodine Content of Iodized Salt

Country	Concentration of Potassium Iodine	100 μg. Iodide Contained in:
United States	1:10,000	1. gram
New Zealand	1:20,000	2. grams
England	1:50,000	5. grams
Switzerland	1:100,000	10. grams
Poland	1:200,000	20. grams

In a few countries iodination of salt is required by law, in some including the United States use of iodized salt is voluntary and dependent upon education and publicity for its adoption. There remain vast populations of the world, some with very high incidences of goiter, with no practical solution to the problem of iodine supplementation.

Role of Iodine in the Body

The vast quantity of iodine in the lowly forms of marine animal life, the sponges, sea fans and corals, suggests a phylogenetic origin for the vertebrate

thyroid hormone, but the role of iodine in these forms has remained singularly obscure. Most of the iodine is contained in tyrosine derivatives which are an integral part of the tough structural protein skeleton. Little is known of the iodine compounds of higher animals up to the vertebrates; and even in fish where the thyroid gland and its hormone thyroxine first emerge, no definite role for the thyroid hormone has been found. In the higher vertebrates from frog to man thyroxine is essential to existence and plays a double role; it is somehow required for normal development and in an equally obscure way it influences the function of most tissues. The thyroid gland seems to have arisen for the sole purpose of providing the organism with thyroxine in proper amounts. Perhaps when all animals lived in the sea where iodine is relatively abundant no thyroid gland was needed, but it is anomalous that the gland should have made its appearance in fish before it was needed for terrestrial existence.

Iodine is absorbed from the intestinal tract usually in the form of iodide ion; if other forms of the element are consumed they must be converted to iodide before they can be used by the thyroid gland, and except for certain organic iodine compounds the conversion takes place before absorption or soon thereafter. Iodide is typically an extracellular ion but is distributed in the body in a larger "space" than is accounted for by the extracellular fluid. The larger volume of distribution is to be explained by the fact that several organs concentrate it. Like the thyroid gland, the salivary glands, stomach, mammary gland, and placenta concentrate iodide; consequently the fluids in the upper portion of the intestinal tract, the milk and fetal blood may contain five to thirty times as much iodide as does the general circulation. The thyroid gland is highly specialized for processing iodide; it has an efficient mechanism for collecting iodide ion from the blood and a still more efficient system for oxidizing this ion and iodinating tyrosine. When an iodine deficiency is instituted the rate of hormone secretion remains constant at first but the iodine stores within the gland suffer depletion. The thyroid, in some manner not yet well understood, senses the deficiency in iodine stores, becomes activated, and extracts iodide from the blood more efficiently (15, 16). This local compensation may be fully effective and hormone secretion may continue at a normal rate. If iodine deficiency becomes more severe, depletion of the gland's stores may eventually be so advanced that the concentration of thyroxine in the blood tends to fall. The pituitary gland detects a decreased concentration of thyroxine and secretes a larger quantity of thyrotropin. In response to this the activity of the thyroid gland is further increased, its cells enlarge, more blood flows, and the whole gland may enlarge. So efficient are these adaptive measures that it is most difficult if not impossible to reduce

thyroxine synthesis to the point of detectable hypothyroidism by artificially restricting dietary iodine.

Much work on artificial iodine deficiency in the rat dating from the work of Remington and collaborators in 1933 (13) has made use of diets which did not permit proper growth because of inadequate protein content or the lack of other essential factors. Nutritious diets have more recently been prepared which are low in iodine and which permit normal growth. In one such study (14) rats were fed for three successive generations on a diet containing only 25 μg. of iodine/Kg. Though goiters developed, growth, development, pregnancy, and lactation were entirely normal. Increasing the iodine content of the diet to 100 to 225 μg./Kg. prevented the goiter but growth and development were not further enhanced by the supplement. It would seem clear, therefore, that even in the face of a very low iodine intake the enlarged thyroids could cope successfully with the deficiency and make adequate amounts of thyroxine.

Under normal circumstances iodide reaching the thyroid is combined with tyrosine at such a rapid rate that virtually no free iodide ion has a chance to accumulate within the gland. For this reason the rate-determining step in hormone formation is thought to be the iodide-collecting process (16) and not one of the subsequent steps along the road to the finished product thyroxine.

It is not difficult to understand that when iodine sources are meager, interference with the iodide-collecting mechanism would grossly alter thyroid function. Thiocyanate (17) and a limited number of other ions such as perchlorate (18) render the gland incapable of concentrating iodide efficiently. Whereas normally the responses to iodine deficiency fully compensate, thiocyanate renders them futile—even a large vascular goiter is incapable of collecting sufficient iodide to prevent the development of myxedema. The situation is corrected by removing the inhibitor or by supplying adequate amounts of iodide. In the latter instance the concentration of iodide in the blood rises to the point where the thyroid can obtain enough of it even without a properly functioning collecting system.

A question needing further study is whether sufficient thiocyanate is derived from natural sources to cause embarrassment to the thyroid's iodide-collecting system, or in other words, enough to increase the daily iodine requirement. Thiocyanate occurs in many vegetables and fruits but the quantity is usually very small and probably insignificant. A more abundant source is from organic cyanides; the so-called cyanogenetic glycosides are widely distributed in the vegetable kingdom and these give rise in the body to cyanide which is efficiently detoxified by conversion to thiocyanate. Vari-

able amounts of thiocyanate can be detected in human blood and urine, more is found after eating almonds, peaches and similiar foods, and more is present in those who smoke tobacco. Cows' milk often contains it because like iodide it is concentrated by the mammary gland and there may be significant quantities in milk after grazing on clover or brassica plants.

Antithyroid Compounds

Another site of interference with iodine metabolism in the thyroid gland is the one already alluded to, concerned with the binding of iodine to protein—the first step in hormone synthesis. It has already been seen that the gland concentrates iodide ion. Next, it oxidizes this to a form equivalent to elemental iodine which then promptly unites with tyrosine groups which are abundantly present in the thyroid protein. This large protein thus comes to contain first monoiodotyrosine and then diidotyrosine. Two molecules of the latter condense to form thyroxine, and the protein, now containing all three iodinated amino acids firmly bound within its structure, is stored in the thyroid follicles as thyroglobulin. It is envisioned that this protein, like many others, is composed of long chains of amino acids arranged in a long twisted chain something like a spiral staircase, with the side groups of the amino acids protruding through the banisters. To account for the ready formation of thyroxine it is supposed that the tyrosyl groups occur in a repetitive fashion, perhaps one for each turn of the spiral, and that two atoms of iodine on each tyrosine facilitate their coupling when they are so disposed in space. Little is known of this coupling process and no compounds are known which specifically interfere with it. The former step, however—oxidation of iodide and formation of iodotyrosines—is specifically inhibited by a large number of substances, the so-called antithyroid compounds (19). These are made up of the various derivatives of thiourea and thiouracil such as those used in the treament of hyperthyroidism, aniline derivatives such as the sulfonamides, and a variety of polyphenols such as resorcinol.

No one has succeeded in extracting from thyroid tissue the enzyme which oxidizes iodide but indirect evidence has led to the current consensus that the oxidation is brought about by hydrogen peroxide and that a peroxidase catalyzes the reaction. The strongest evidence in favor of this theory derives from the fact that all of the several types of compound which interfere with thyroxin synthesis in the thyroid also interfere in one way or another with oxidative systems of the peroxidase type (20, 21).

Antithyroid compounds impose a much more difficult problem to the thyroid than do inhibitors of the thiocyanate type. When a sufficient quantity of thiouracil or related compound is present, no amount of added iodide can

overcome the inhibition and promote hormone synthesis. Of particular interest to the problem of iodine nutrition, however, is the fact that the lower the iodine intake the larger and less efficient the goiter resulting from administration of an antithyroid drug. Conversely, an increased intake of iodine reduces the goitrogenic effect of these compounds and if the compound is taken in small amounts only, added iodine can overcome the inhibition of hormone synthesis. In a recent study (22), for example, in rats fed a diet containing only 20 μg./Kg. of iodine to which was added 50 mg./Kg. of thiouracil, goiter was completely prevented by the administration of small amounts of iodine. Similarly failure of growth, from deficient thyroxine synthesis, could be completely overcome by increasing the dietary iodine even when the diet contained as much as 250 mg./Kg. of thiouracil.

It has long been known that ingestion of certain foods would lead to thyroid enlargement even without iodine deficiency, and it is now known that some vegetables contain *1*-5-vinylthiooxazolidone, an antithyroid compound similiar to thiouracil. Fortunately this compound occurs only in members of the mustard family, is concentrated largely in the seeds, and to affect the thyroid the vegetables must be eaten raw. It would seem unlikely therefore that the brassica plants would be an important or frequent cause of goiter (24). Whether or not other and more commonly used foods contain goitrogenic materials is a question which deserves further study.

Other Factors Influencing Iodine Requirement

Mention has been made of the fact that goiter from thiocyanate or from small amounts of antithyroid compound can be prevented by increasing the iodine intake. In one sense, then, these agents can be thought of as increasing the iodine requirement. Because added iodine in a given situation reduces the incidence of goiter in a population, or reduces the thyroid enlargement of experimental animals it does not necessarily follow that iodine deficiency was the primary goitrogenic influence.

Doubtless there are many factors which influence the iodine requirement but only a few have been clearly delineated. The rate of loss of iodine from the body is, of course, the final determinant of the required intake. In most mammals including man the major excretory loss is renal; the kidney seems to have little control over the rate but rather excretes a fixed proportion of that presented to it. In some animals, such as the dog, a larger proportion of the blood iodide is excreted when the concentration in the blood is high (25) and in such animals as the dog (25), mouse (26), and rat (27) added chloride greatly increases the renal excretion of iodide. So prominent is this influence in the mouse (26) and rat that diets very low in iodine only

become goitrogenic when chloride in the diet is increased. This effect has not been seen in man but electrolyte disturbances in man sometimes are associated with disturbed iodine metabolism as indicated by enhanced uptake of radioactive iodine by the thyroid.

Increased or decreased flow of blood through the kidney correspondingly increases or decreases renal excretion of iodine, and some of the abnormalities of iodine metabolism seen clinically may be so mediated. The high content of iodide in saliva and gastric juice suggests vomiting as one cause of iodine depletion.

There is evidence from animal experiments that certain foods may reduce the iodine requirement. In earlier work frequent reference was made to "antigoitrogens" in food but we do not know what these substances could be. Aside from iodine the only true antigoitrogen is thyroid hormone. Unlike iodine, thyroid hormone will prevent goiter from any cause, even from full doses of an antithyroid compound. It is believed that foods of animal origin, especially meat (28) and milk, may contain small amounts of thyroid hormone or a derivative thereof. It has been found, for example, that inclusion of casein in low iodine diets fed to mice (29) or to rats (30) prevents goiter, and that feeding meat to dogs whose thyroids had been completely destroyed with radioactive iodine prevents the full development of myxedema (31).

Another factor clearly influencing iodine requirement is environmental temperature. The thyroid gland has long been known to be activated by cold and suppressed by heat; it now appears that this change is mediated by an increased rate of destruction of thyroxine upon exposure to cold (32, 33). The pituitary gland responds to the lowered blood concentration of thyroxine by secreting more thyrotropin which in turn activates the thyroid sufficiently to restore equilibrium. When thyroxin is destroyed in the body, its content of iodine is again available for use, but as the kidneys normally remove twice as much iodide from the blood as the thyroid does, the net effect of cold is to increase the loss of iodine from the body.

It has long been supposed that the need for thyroid hormone and consequently the iodine requirement must be increased during puberty and pregnancy in order to account for the prevalence of goiter at those periods. With respect to puberty there is no conclusive evidence on this point; but during pregnancy the concentration of thyroxine in the blood increases. As the fetus must derive its stores of iodine from the mother, the mother's requirement is thus increased. During lactation iodide is lost in the milk. Assuming a blood concentration of 0.3 μg. of iodide per 100 cc. and a concentration by the mammary gland of 25-fold, each 100 cc. of milk would

contain 7.5 μg. This would double the minimal iodide requirement at the time of maximal lactation. Whether the iodine requirement is altered by menstruation, menopause, infections, or other illness remains undetermined.

For centuries consumption of excess calcium or the hardness of drinking water have been held responsible for an increased tendency to goiter and, inferentially, to a reduced efficiency of iodine utilization. Though a positive role of calcium in the genesis of goiter has repeatedly received experimental support in recent times, the mechanism is obscure and indeed the effect has not been firmly established. Among the many factors which have from time to time been suggested as favoring the development of goiter or increasing the need for iodine may be mentioned the following: polluted drinking waters and those containing excessive quantities of one or another mineral substance, excess consumption of milk, meat or various vegetables, vitamin deficiency or excess arsenic, cobalt, bromine and fluorine, and finally iodide itself.

Effects of Excess Iodine

It has been noted that when the daily intake of iodine falls much below 100 μg. daily the thyroid becomes activated and may enlarge. With quantities between 100 and 1000 μg. daily the thyroid seems to function efficiently but with larger amounts, 5 mg. daily or more, some remarkable changes are sometimes seen. The well-known but poorly understood therapeutic response of hyperthyroidism to iodine can be brought about by quantities in this range; the enlargement, activity, and vascularity of the gland all are suppressed and the patient improves. When iodine is taken in excess by normal individuals the response is variable and unpredictable. In many individuals the thyroid seems to be unaffected but in some the gland's function is suppressed to the point of hypothyroidism and goiter results (34, 35, 36, 16). When the offending agent is discovered and removed, thyroid function returns to normal and the goiter subsides. Excess iodine taken by individuals with simple goiter sometimes leads to further thyroid enlargement and rarely to hyperthyroidism. Seldom is iodine alone an effective remedy for goiter.

Prolonged ingestion of large amounts of iodine leads to the appearance in the blood of an organic form of iodine which behaves like thyroxine in the useful clinical test for thyroid function, the determination of the protein-bound iodine of the serum (37). A mistaken diagnosis of hyperthyroidism may be made if the patient and physician are unaware of the large intake of iodine. Conversely, excess iodine suppresses the uptake of radioactive iodine by the thyroid and a diagnosis of myxedema may erroneously be entertained.

Sources of excessive quantities of iodine are mostly man-made. It is

unlikely that ingestion of natural foods or waters would provide too much iodine even if sea foods seasoned with American iodized salt and mineral waters made up most of the diet. The commonest source is medicinal. Many remedies contain iodine, either as the chief active ingredient or as an incidental addition to a mixture, and frequently neither the patient nor the physician is aware that the medicine contains iodine. A recent compilation of iodine-containing pharmaceuticals listed several hundred different types marketed under more than a thousand different names (38). Common disorders treated with preparations of iodine include asthma, cough, heart disease, arteriosclerosis, arthritis, skin diseases, and parasitic infestations. Iodine is a main constituent of media used in x-ray diagnosis, of various antiseptics and ointments, and is added to many patent medicines, vitamin preparations, dentifrices, and cosmetics. The problems thus posed to the student of human thyroid function and to the physician dealing with thyroid disorders is readily appreciated.

Iodine Deficiency, Goiter, Cretinism

For more than a century there have been proponents of the concept of iodine deficiency as the cause of goiter, but throughout this time there have been those who believed other causes to be responsible (39). Even today faced with extensive data upon which to form an opinion it must still be concluded that the problem is not yet entirely settled.

Experimental production of goiter in animals, chiefly rats and mice, by feeding diets low in iodine indicates that goiter can result from iodine deficiency. Objection to this type of evidence derives from the fact that the protein in these diets must be largely of vegetable origin in order to keep the iodine content low, and it may be questioned whether the diets are entirely free of goitrogenic substances such as thiocyanate or antithyroid compounds. The fact that small amounts of added iodine prevent the goiter does not settle the problem because, as already seen, the goitrogenic action of small amounts of these agents can be overcome by small iodine supplements.

Recent studies using modern technics of iodine analysis and radioactive tracer iodine have indicated that in certain endemic goiter areas the intake of iodine is indeed very low. In the careful study of the goiter in Mendoza, Argentina (40), it was found that the daily excretion of iodine in the urine averaged 57 μg. indicating that the daily intake averaged only about one-half of the estimated minimal requirement. Though a number of the subjects studied excreted less than 20 μg. day, no manifestations of hypothyroidism were seen; there was a rapid uptake of radioactive iodine, and

the concentration of thyroxine in the blood was normal, indicating again how efficiently the enlarged thyroid can compensate for a very low iodine intake. Similiar studies conducted in a goitrous region in Venezuela (41) have indicated the strong possibility that iodine intake there is also very low. The accumulation of radioactive iodine by the thyroid gland was noted to be rapid and to average 85% of the tracer dose; this high uptake was noted whether or not there was a goiter. Some of the newly accumulated iodine could be discharged by perchlorate, from the enlarged but not from the normal thyroid glands, suggesting to these investigators that the process of organic binding of iodine by the goiters was deficient. The possibility that some form of antithyroid agent was contributing to the goiter is raised by these findings.

Analyses of the goiter areas of Central America have indicated a high incidence in children and adults living in non-urban areas of El Salvador, Honduras and Panama, even though there is no clear evidence of iodine deficiency (42, 43). The crude sea-salt used was found to contain an average of 0.22 parts of iodine per 10,000 (cf. 1:100,000 in European, and 1:10,000 in American iodized salt) or 22,000 μg./Kg. Four or five grams of this salt would provide an ample daily supplemental and one must conclude that either little salt was used or that some other factor contributed to an increased requirement. It is of especial interest therefore that administration of iodine proved to be an effective remedy in a large proportion of the school children in these areas (44).

Studies extending over the past six or seven years on goiter in Tasmania (45) have shown that a high incidence of goiter in school children was not reduced by the administration of a weekly supplement of iodine. These recent findings are in striking contrast to the earlier results of iodine prophylaxis in the United States (46), Switzerland (47), and New Zealand (48), and suggest again that while iodine deficiency is a major cause of endemic goiter, it may not be the only cause and that the principal etiologic factor may not be the same in all endemic goiter areas.

The most pressing reason for undertaking measures to prevent goiter is not so much the goiter itself but the concomitant cretinism of goitrous populations. Apparently the human fetus derives little if any thyroid hormone from the mother during intrauterine life and must make its own. If sufficient iodine is not available, or if the mother is under some other goitrogenic influence, the fetus, lacking thyroxine, fails to develop normally. The physical retardation can be corrected by the administration of thyroid hormone but the mental retardation is irreversible and permanent. After birth the infant may derive adequate iodine from milk but there is evidence that irreparable damage may have already occurred. A second reason for pre-

venting goiter is to obviate surgical operations upon the thyroid gland and the attendant discomfort, expense, and complications. The goiter which formerly may have been barely able to supply sufficient thyroxine will often be unable to do so if partially removed.

Simple goiter in regions such as New England which are not usually regarded as endemic goiter areas does not seem to be due to insufficient iodine. Unlike the goiter seen in some iodine-deficient regions (40), it is sometimes associated with hypothyroidism. Sometimes a causative factor can be found but in the vast majority of cases the cause remains completely obscure.

It may be concluded that one of the major causes of simple goiter is the iodine deficiency which affects large populations of the world and that proper supplementation of the iodine intake could materially reduce the incidence of goiter and cretinism in many regions. Provision of small daily quantities of iodine, as in iodized salt, is probably a better measure than the administration of larger amounts at longer intervals. Consumption of large quantities of iodine is sometimes harmful and it would be desirable if iodine-containing remedies were so labelled. There are factors other than iodine deficiency that can contribute to the causation of goiter. Further work is urgently required to determine the cause when a lack of iodine seems not to be responsible. Finally, it may be noted that thyroid hormone in adequate amounts is often an effective remedy and that iodine is more effective in preventing goiter than in curing it.

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